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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,127	SHIE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *120-122,126,128,130,132-135 and 139-145* is/are pending in the application.

4a) Of the above claim(s) *126,128,130 and 135* is/are withdrawn from consideration.

5)☒ Claim(s) *120,122 and 144* is/are allowed.

6)☒ Claim(s) *121,132-134,139-143 and 145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix I*.

DETAILED ACTION

This action is in response to the amendment, filed 2/16/2010, in which claims 123-125, 127, 129, 131 and 136-138 were cancelled, claims 120, 121, 132 and 134 were amended, and claims 139-145 were newly added. Claims 120-122, 126, 128, 130, 132-135 and 139-145 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group I with traverse in the reply filed on 8/4/2009. The restriction between Groups I and II was withdrawn in the Office action mailed 10/29/2009.

Claims 126, 128, 130 and 135 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/4/2009.

Currently, claims 120-122, 132-134 and 139-145 are under consideration.

Response to Arguments - Claim Objections

The objection of claim 134 has been withdrawn in view of Applicant's amendment to the claim in the reply filed 2/16/2010.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 121, 139 and 140 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the reply filed 2/16/2010, claim 121 was amended to limit the method of claim 120 tow where RTEF-1 polypeptide "has at least 90% identity to the sequence of SEQ ID NO: 4." Claims 139 and 140 depend from claim 121.

Claim 120 requires the RTEF-1 polypeptide to have at least 85% identity to the sequence of SEQ ID NO: 7. SEQ ID NO: 7 is a 434 amino acid protein. Claim 121 requires 90% sequence identity to the sequence of SEQ ID NO: 4. However, this sequence is a 50 nucleotide sequence. The specification discloses that the sequence of SEQ ID NO: 4 is a VEGF promoter sequence (e.g., page 19, lines 7-9).

The response, filed 2/16/2010, asserts that support for the amendment can be found in the specification at page 14, lines 21-27, page 24, lines 12-19, page 28, lines 25-27 and Figure 13. However, these portions of the specification do not provide support for a polypeptide with identity to the nucleic acid sequence of SEQ ID NO: 4.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the passages that Applicant has provided do not provide support.

Claims 121, 134, 139 and 140 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing angiogenesis in a mammal, and a method of treating or reducing hypoxia in a mammal, comprising providing within or adjacent to tissue in need thereof in said mammal a therapeutically effective amount of Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide, or a nucleic acid molecule encoding said polypeptide, wherein said RTEF-1 polypeptide has at least 85% sequence identity to the sequence of SEQ ID NO: 7, does not reasonably provide enablement for the use of any polyoma vector; the use of a papilloma vector, or the ability to make and use an RTEF-1 polypeptide with at least 90% identity to the nucleic acid sequence of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was made in the Office action mailed 10/29/2009 and has been rewritten to address the amendments to the claims in the reply filed 2/16/2010.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 121, 139 and 140 are drawn to increasing angiogenesis in a mammal. The claims are drawn to the step of providing within or adjacent to tissue in need thereof in the mammal a therapeutically effective amount of Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide or a nucleic acid molecule encoding said polypeptide, where said RTEF-1 polypeptide has angiogenic activity and at least 85% sequence identity to the sequence of SEQ ID NO: 7 and at least 90% identity to the nucleic acid sequence of SEQ ID NO: 4. Claim 139 further requires the polypeptide to have 95% identity to the sequence of SEQ ID NO: 7. Claim 140 requires the polypeptide to comprise the sequence of SEQ ID NO: 7. The nature of the invention is complex in that the claims require a polypeptide to have identity with a nucleic acid sequence.

Claim 134 is drawn to treating, or reducing hypoxia in a mammal at risk for or experiencing hypoxia. The claim is drawn to the step of providing within or adjacent to tissue in need thereof in the mammal a therapeutically effective amount of RTEF-1 polypeptide or a nucleic acid encoding said polypeptide, where the RTEF-1 polypeptide has at least 85% sequence identity to the sequence of SEQ ID NO: 7, and wherein the nucleic acid molecule is a viral expression vector selected from the group consisting of an adenovirus, retrovirus, adeno-associated virus vector, herpes simplex virus, SV40 vector, polyoma virus vector, papilloma virus vector, picornavirus vector, and vaccinia virus vector. The nature of the invention is complex in that the viral expression vector must be delivered in an amount sufficient to increase angiogenesis, treat or reduce hypoxia, or prevent hypoxia.

Breadth of the claims: The claims broadly encompass the use of any polyoma viral expression vector and any papilloma viral expression vector.

Guidance of the specification and existence of working examples: The specification discloses the sequence of human RTEF-1 as SEQ ID NO: 7. In preliminary studies, Applicant found that the expression of RTEF-1 was increased three-fold in endothelial cells cultured under hypoxic conditions. To confirm this observation, Northern blot analysis was performed to measure the time-dependent level of RTEF-1 mRNA in RNA isolated from bovine aortic endothelial cells (BAEC) cultured under hypoxic conditions (<1% O_2) (e.g., page 43, lines 15-20). Figures 1A and 1B show that RTEF-1 is induced by hypoxia and that such expression peaked about 6 hours following exposure to hypoxia. Further, it was demonstrated that RTEF-1 overexpression in BAEC cells by transfection of RTEF-1 cDNA resulted in the upregulation of VEGF expression (e.g., page 43, lines 22-28; Figures 2A and 2B). VEGF expression is induced by hypoxia, but is further induced by RTEF-1 (e.g., page 43, lines 26-28). Further, RTEF-1 was shown to enhance VEGF promoter activity under hypoxic conditions (e.g., page 47, lines 13-23; Figure 7). Based on these observations, Applicant proposed that RTEF-1 may play a role in promoting the expression of VEGF by regulating its promoter activity, particularly in hypoxic conditions.

Using a promoter assay, Applicant determined that possible gene regulatory elements within the VEGF promoter necessary for RTEF-1 activation are located between -194 and -66 of the VEGF sequence (e.g., page 44, lines 16-18; Figures 2 and 3). This region of the VEGF promoter demonstrated a dose response increase in promoter activity with increasing amounts of RTEF- (e.g., paragraph bridging pages 44-45; Figure 4). Further mutation analysis identified the

Sp1-I binding domain (-97 to -87) of the VEGF promoter as being required for the stimulation by RTEF-1 (e.g., pages 45-47).

Next, the ability of RTEF-1 to accelerate cellular proliferation and the formation of a vascular structure, via transactivation of VEGF, was tested in BAEC cells overexpressing RTEF-1. These cells demonstrated a faster growth rate compared with wild-type or vector transfected BAEC cells (e.g., page 48, lines 1-6; Figure 8). Further, ring and cord formation was visible in the RTEF-1 stably transfected BAEC but not in control cells after 48 hours of culture on growth factor-reduced Matrigel® (e.g., page 48, lines 7-11; Figure 8).

In addition to regulating the expression of VEGF, the specification demonstrates that RTEF-1 is capable of stimulating the expression of FGFR1 and COX-2. RTEF-1 overexpression increases FGFR1 promoter activity in BAEC cells (e.g., paragraph bridging pages 48-49). The promoter activity was localized to an SP-1-like element in the FGFR1 promoter (e.g., paragraph bridging pages 48-49; Figure 9). RTEF-1 overexpression stimulates COX-2 promoter activity over three-fold in BAEC (e.g., page 49, lines 7-21; Figure 11).

There are no working examples of the claimed invention. Example 10 of the specification is a prophetic example directed to the use of a recombinant adenovirus construct to express RTEF-1 in mouse heart to assay the physiological effects of RTEF-1 expression on the relative angiogenic factors *in vivo*. Example 11 of the specification is a prophetic example directed to the *in vivo* delivery of a recombinant adenovirus or adeno-associated virus to patients diagnosed with coronary artery disease or peripheral vascular disease for treatment. The specification envisions increasing neovascularization or angiogenesis in these patients by

inducing VEGF, FRGFR1, and COX-2 expression in vascular endothelial cells. Example 12 is a prophetic example directed to combination therapy using RTEF-1 and HIF-1α.

The use of RTEF-1 to stimulate VEGF, FGFR1 and COX-2 expression in endothelial cells is the basis for the claimed invention (e.g., page 23, lines 8-11). The specification teaches that VEGF is one of the most promising angiogenic ligands targeted in the art for therapeutic purposes. VEGF receptors are typically upregulated under ischemic conditions and the administration of recombinant VEGF has been shown to augment the development of collateral vessels and improve the function of peripheral and myocardial ischemic tissues (e.g., page 1, lines 15-30). Further, the specification teaches that FGF is a potent endothelial cell mitogen which increases the survival and proliferation of endothelial cells (e.g., paragraph bridging pages 1-2). The specification teaches that COX-2 is another factor involved in normal angiogenesis, as wells as tumor-associated angiogenesis (e.g., page 2, lines 3-6).

The specification asserts that RTEF-1 can be useful to treat, reduce or prevent conditions caused by hypoxia, and can be used to promote angiogenesis by increasing blood vessel growth in a mammal (e.g., page 2, line 21 to page 3, line 8). The specification envisions the treatment, reduction or prevention of ischemic conditions including cardiac infarction, chronic coronary ischemia, chronic lower limb ischemia, stroke, cerebral ischemia, peripheral vascular disease, myocardial ischemia, myocardial infarcts, unstable angina, cardiac hypertrophy, arrhythmia, cardiomyopathy, angina pectoris, atherosclerosis, arteriosclerosis, a complication of diabetes, restenosis, organ hypertrophy, organ hyperplasia, septic shock, inflammatory disease, and myocardial dysfunction (e.g., page 4, lines 22-29; paragraph bridging pages 24-25). The specification envisions the prophylactic use of RTEF-1 in the anticipation of an ischemic

condition, such as with a surgical procedure or trauma (e.g., paragraph bridging pages 4-5; page 26, lines 1-11).

With regard to the administration of RTEF-1 protein, the specification envisions the use of cell therapy methods such as microinjection or transduction. The specification envisions using local or systemic administration (e.g., page 25, lines 15-19). The specification defines "RTEF-1" to mean any polypeptide that exhibits an activity common to its related, naturally occurring RTEF-1 polypeptide. Thus, the specification envisions using any amino acid sequence with RTEF-1 activity. The claims require at least 60% or at least 80% identity to Accession Numbers AAC50763, Q62296 or P48984 (e.g., page 14, lines 21-27); however, the specification only teaches the sequence of AAC50763 (SEQ ID NO: 7). At page 9, lines 24-32, the specification states the following with regard to determining angiogenic activity:

> Angiogenic activity may be determined in *vitro* by measuring, for example, endothelial cell proliferation, endothelial cell migration, endothelial cell survival, and tubule formation. Alternatively, angiogenic activity may be determined in *vivo,* by counting or staining vessels, or alternatively, by quantitating functional vessels, using the MATRIGEL® assay, corneal micropocket assay, hind limb ischemic model, and chick chorioallantoic membrane (CAM) assay. Preferably, in *vitro* assays measure endothelial cell proliferation or survival and preferred *in vivo* assays are the hind limb ischemic model and the corneal micropocket assay. For the purpose of determining claim scope, the preferred assay is hind limb ischemic model.

With regard to the administration of a nucleic acid molecule encoding RTEF-1, the specification envisions the use of a plasmid vector or a viral vector, where the viral vector is an adenovirus, retrovirus, adeno-associated virus, herpes simplex virus, SV40, polyoma virus, papilloma virus, picornavirus, or vaccinia virus (e.g., page 4, lines 13-17). The specification envisions using a tissue-specific promoter to direct expression of RTEF-1 in endothelial cells, cardiomyocytes, skin cells, hepatocytes, myocytes, adipocytes, fibroblasts, or any tissue (e.g.,

page 4, lines 17-21; page 36, line 28 to page 37, line 25). The specification envisions using local or systemic administration (e.g., page 25, lines 15-19). General techniques regarding the *in vivo* or *ex vivo* administration of nucleic acid are discussed at page 28, line 30 to page 30, line 2 and page 31, line 11 to page 32, line 25).

With regard to SEQ ID NO: 4, the specification teaches that it is a nucleic acid sequence from the VEGF promoter (e.g., page 19, lines 7-9).

Predictability and state of the art: It would be unpredictable to use any polyoma vector, papilloma virus vector, or picornavirus vector for gene therapy. Strayer (Journal of Cellular Physiology, Vol. 181, pages 375-384, 1999, cited in a prior action) teaches that the shortcomings of gene therapy in meeting its goals largely reflect limitations of the vectors that have been used to deliver the gene therapy (e.g., page 375, right column, 2nd paragraph). SV40 is one member of the family of *polyomaviridae* (Ehrhardt et al. Current Gene Therapy, Vol. 8, pages 147-161, 2008, cited in a prior action; e.g., page 151, left column, 1st full paragraph). The prior art teaches that SV40 vector suitable for gene therapy applications (Strayer, DS. Journal of Cellular Physiology, Vol. 181, pages 375-384, 1999, cited in a prior action; Strayer et al. Current Opinion in Molecular Therapeutics, Vol. 4, No. 4, pages 313-323, August 2002, cited in a prior action). Neither the specification nor art of record teach the use of any other polyoma vector for gene therapy. The art does not teach the use of papilloma virus vectors for gene therapy. Ehrhardt et al teach that bovine papillomavirus (BPV) belongs to the family of *papillomaviridae*, but is not suitable for use in gene therapy applications, because it is known to cause cellular immortalization (e.g., page 151, right column The BPB (Intermediate Copy Number) Plasmid Replicon)). There is no art on the record that indicates it would have been routine in the art at

the time the invention was made to make and use papilloma viruses for gene therapy applications.

It would have been unpredictable to make and use a polypeptide defined, in part, by percent identity to a nucleic acid sequence. The building blocks of proteins (i.e., amino acids) and the building blocks of polynucleotides (nucleic acid moieties) are structurally and functionally distinct.

Amount of experimentation necessary: The quantity of experimentation required to carry out the full scope of the claimed invention is large. One would be required to develop polyoma, and papilloma expression vectors suitable for gene therapy. Furthermore, a large amount of experimentation would be required to determine how to make and use a polypeptide defined, in part, by percent identity to a nucleic acid sequence.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 121, 134, 139 and 140 are not considered to be fully enabled by the instant specification.

Response to Arguments - 35 USC § 112

Applicant's arguments, see pages 16-18, filed 2/16/2010, with respect to the rejection of claims 120, 122 and 132-134 under 35 U.S.C. 112, first paragraph (written description), have been fully considered and are persuasive. The specification notes that regions of RTEF-1 that have structural significance for biological function include the DNA binding domain at the amino-terminal end of RTEF-1 as discussed in Ueyama et al (Journal of Biological Chemistry,

Vol. 275, pages 17476-17480, 2000). Ueyama et al teach that the DNA binding domain of RTEF-1 and TEF-1 are 100% identical (e.g., page 17476, right column; Figure 1). Ueyama et al teach that the STY domain is a region rich in serine, threonine and tyrosine residues (e.g., page 17479, paragraph bridging pages 17479-17480). The teachings of Appukuttan et al provide post-filing evidence of the accuracy of the statements made in the specification. Variants of RTEF-1 containing the DNA binding domain and STY domain are sufficient for activation of transcription from the VEGF promoter (e.g., Figures 2 and 4, especially the 936 bp isoform). The previous rejection of claims 120, 122 and 132-134 has been withdrawn.

With respect to the rejection of claims 121, 134, 139 and 140 under 35 U.S.C. 112, first paragraph (scope of enablement), Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response does not provide any remarks directed to the newly added requirement that the RTEF-1 polypeptide be at least 90% identical to the nucleic acid sequence of SEQ ID NO: 4.

With regard to the polyoma and papilloma virus vectors of claim 134, the response asserts that the several publications describe the generation or use of polyomavirus and papillomavirus vectors. The response provides copies of abstracts of Touzé et al (2001), Sasnauskas et al (2002), Tegerstedt et al (2005), Georgens et al (2005), Krauzewicz et al (2000), Krauzewicz and Griffin (2000), Khan and Sverdrup (1997) (pages 117-118), Tammur et al (2005), and Sarver et al (1981). The response asserts that the use of these vectors in the present method is well within the purview of one of skill in the art.

These arguments are not found persuasive. The references do not demonstrate that the use of polyoma virus expression vectors (other than SV40) were well within the purview of one

of skill in the art. The claim requires the nucleic acid molecule encoding the RTEF-1 polypeptide to be in an expression vector that is a viral vector, where the viral vector is a polyoma virus vector. Thus, the nucleic acid sequence encoding RTEF-1 must be inserted into the polyoma nucleic acid vector. The references cited in the response demonstrate the use of polyoma polypeptides for nucleic acid delivery. However, these references do not appear to teach the use of the polyoma nucleic acid as an expression vector as required by the claims. For example, Touzé et al teach that polyomavirus protein can be expressed from a recombinant baculovirus expression vector. Touzé et al teach that the polyomavirus protein could be used to package plasmid nucleic acid molecule. Applicant has not provided evidence that polyoma viral vectors (other than SV40) can be used as viral expression vectors for cloning and expression of a nucleic acid sequence encoding RTEF-1 polypeptide for therapeutic purposes. With regard to the papilloma viruses, the art cited in the response teaches that papilloma viruses induce benign proliferative squamous epithelial and fibro-epithelial lesions (warts and papillomas) in their natural hosts (Khan and Sverdrup (1997); e.g., page 117). The Tammur et al (2005) and Sarver et al (1981) references do not teach the use of papilloma viral expression vectors for *in vivo* therapeutic applications. Tammur teaches that *in vivo* experiments are required to determine if the *in vitro* results are correlated with clinically significant results. Furthermore, the art cited in the rejection of record indicates that bovine papillomavirus (BPV) belongs to the family of *papillomaviridae*, but is not suitable for use in gene therapy applications, because it is known to cause cellular immortalization (Ehrhardt et al). The art cited by Applicant also teaches that human papilloma viruses cause proliferative lesions. Accordingly, one would conclude that these vectors are not suitable for therapeutic applications in humans.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 132-134, 141, 142 and 145 are rejected under 35 U.S.C. 102(b) as being anticipated by Umezawa et al (US Patent Application Publication No. 2002/0142457 A1, cited in a prior action; see the entire reference), as evidenced by the entry for TEAD 4 TEA domain family member 4 [*Homo sapiens*], GeneID: 7004, printed from Entrez Gene on 10/23/2009 as pages 1/7 to 7/7, cited in a prior action). This rejection was made in the Office action mailed 10/29/2009 and has been rewritten to address the amendments to the claims.

The claims encompass a method of treating or reducing hypoxia in a mammal at risk for or experiencing hypoxia, comprising providing within or adjacent to tissue in said mammal a therapeutically effective amount of a nucleic acid molecule encoding Related Transcriptional Enhancer Factor-1 (RTEF-1) protein, where the RTEF-1 protein has at least 85% sequence identity to the sequence of SEQ ID NO:7, which is disclosed as human RTEF-1 (Accession Number AAC50763) in the present specification. Claim 133 limits the nucleic acid molecule to an expression vector selected from the group consisting of a plasmid or a viral vector, and claim 134 limits the viral vector to one such as an adenovirus, retrovirus, or adeno-associated virus.

The present specification discloses that hypoxia is a central feature of pathological conditions involving abnormal vascularization, such as myocardial infarction (e.g., paragraph bridging pages 22-23).

Umezawa et al teach the treatment of ischemic heart diseases such as myocardial infarction comprising locally administering a recombinant virus vector encoding TEF-3 to the myocardium using a catheter or the like so that the virus can be absorbed into the myocardium of the patient (e.g., paragraphs [0150]-[0152], [0157]-[0160], [0165]-[0178]). Umezawa et al teach the method where the virus vector is an expression vector (e.g., paragraphs [0169] and [0175]). Umezawa et al teach the method where the recombinant viral vector is a retrovirus, lentivirus, adenovirus, or adeno-associated virus (e.g., paragraphs [0167]-[0172]). Umezawa et al teach the method where TEF-3 encoding nucleic acid molecule has the sequence of SEQ ID NO: 28, which encodes the protein of SEQ ID NO: 27 (e.g., paragraph [0165]).

The sequence of Umezawa et al is at least 96.5% identical to the amino acid sequence of SEQ ID NO: 7 (a.k.a. Accession No. AAC50763). See the alignment attached to the Office action mailed 10/29/2009 as Appendix I. The Entrez Gene entry for TEAD 4 TEA domain family member 4 is cited only to show that RTEF-1 is also known as TEF-3 (e.g., page 1/7). Because the TEF-3 protein of Umezawa et al is an RTEF-1 protein, it would necessarily have angiogenic activity.

Response to Arguments - 35 USC § 102

With respect to the rejection of claims 132-134, 141, 142 and 145 under 35 U.S.C. 102(b) as being anticipated by Umezawa et al, as evidenced by the entry for TEAD 4 TEA domain

family member 4 [*Homo sapiens*], GeneID: 7004, printed from Entrez Gene, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that Umezawa fails to teach or suggest providing an RTEF-1 polypeptide having at least 85% sequence identity to the sequence of SEQ ID NO: 4 within or adjacent to tissue in need thereof in a mammal to treat or reduce hypoxia, and the Examiner indicated that this amendment would overcome the art rejection in a telephonic interview.

This argument is not found persuasive, because the claims require the polypeptide to have at least 85% identity to the polypeptide of SEQ ID NO: 7. The polypeptide taught by Umezawa et al is 96.5% identical (419/434 amino acids) to the polypeptide of Accession No. AAC50763, which is the sequence of SEQ ID NO: 7. See the alignment mailed 10/29/2009.

The response asserts that Umezawa fails to teach the treatment or reduction of hypoxia. This argument is not found persuasive. Umezawa teaches the treatment of ischemic heart disease (e.g., paragraph [0157]), such as myocardial infarction, by administering a viral vector encoding TEF-3 protein (e.g., paragraphs [0150]-[0152], [0157]-[0160], [0165]-[0178]). While the administration of TEF-3 would inherently result in the stimulation of angiogenesis in addition to the cardiomyocyte differentiation disclosed by Umezawa, this new observation by Applicant is not sufficient to overcome the rejection. Further characterization of the prior art method to recognize the concomitant increase in angiogenesis does not make the claims patentable.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 143 is rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al (US Patent Application Publication No. 2002/0142457 A1, cited in a prior action; see the entire reference), as evidenced by the entry for TEAD 4 TEA domain family member 4 [*Homo sapiens*], GeneID: 7004, printed from Entrez Gene on 10/23/2009 as pages 1/7 to 7/7, cited in a prior action), in view of GenBank Accession No. NP_003204 (GI: 4507427, publicly available October 2000; see the entire reference). This is a new rejection, necessitated by the addition of new claim 143 in the reply filed 2/16/2010.

The teachings of Umezawa et al are described above and applied as before.

Umezawa et al do not teach the method where the TEF-3 protein encoded by the viral vector comprises the sequence of instant SEQ ID NO: 7.

GenBank Accession No. NP_003204 teaches the amino acid sequence of TEF-3 protein, which was also known as EFTR-2, RTEF-1, RTEF1, TCF13L1, TEF-3 and TEFR-1 (see the entire reference). The sequence of GenBank Accession No. NP_003204 is 100% identical to the amino acid sequence of SEQ ID NO: 7, which is the sequence of GenBank Accession No. AAC50763 (see the attached alignment in Appendix I).

Because Umezawa et al teach the method where the vector encodes a TEF-3 protein, and GenBank Accession No. NP_003204 teaches a TEF-3 protein, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute one TEF-3 protein for another to achieve the predictable result of providing a method of treating ischemic heart disease resulting from a myocardial infarction using the vector encoding the TEF-3 protein.

Conclusion

Claims 120, 122 and 144 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston
Examiner
Art Unit 1636

/JD/

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636